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Customer No. 22,852
Attorney Docket No. **09757.0003**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
	)
Maria PRAT QUINONES et al.	) Group Art Unit: 1626
	)
Application No.: 10/510,680	) Examiner: Yong Liang Chu
	)
Filed: October 8, 2004	) Confirmation No.: 4960

For: **NEW PYRROLIDINIUM DERIVATIVES**

Mail Stop PGPUB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REQUEST FOR CORRECTED PATENT APPLICATION PUBLICATION UNDER 37 C.F.R. § 1.221(b)

The U.S. Patent and Trademark Office published the above-identified Application No. 10/510,680 as Publication No. US 2005/0282875 A1 on December 22, 2005. The published application contains mistakes that are the fault of the Office and which may be material. Attached hereto are copies of: a) the relevant pages of the originally filed application; b) copies of the relevant pages of the Preliminary Amendment filed on October 4, 2004, on which the claims of the published application are based; and c) a marked-up copy of the pages of the published application containing the mistakes.

A mistake is material when it affects the public's ability to appreciate the technical disclosure of the patent application publication or determine the scope of the provisional rights that an applicant may seek to enforce upon issuance of a patent. *See*

C.F.R. § 1.221(b). The mistakes, which are indicated in red ink on the relevant pages of the marked-up copy of the published application attached hereto, are as follows:

1. In claim 1: in the definition of group A, the fragment reading "A represents a group chosen from –CH2-, -CH=CR7-, -CR7=CH-, -CR7R8-, -CO-, -O-S-, -S(O)-, -S(O)2- and –NR7-, wherein R7" should read "A represents a group chosen from –CH2-, -CH=CR7-, -CR7=CH-, -CR7R8-, -CO-, -O-, -S-, -S(O)-, -S(O)2- and –NR7-, wherein R7".

2. Claim 1: in the definition of group Q, the fragment reading "Q represent a single bond, or a group chosen from $-CH_2-$, $-CH_2-CH_2-$, -O-, $-O-CH_2-$, -S-, $-S-CH_2-$ and –CH=CH" should read "Q represent a single bond, or a group chosen from $-CH_2-$, $-CH_2-CH_2-$, -O-, $-O-CH_2-$, -S-, $-S-CH_2-$ and –CH=CH-".

3. Claim 7: "A compound according to claim 6, wherein A is a group chosen from $-CH_2-$, -CH=CH-, and –O." should read "A compound according to claim 6, wherein A is a group chosen from $-CH_2-$, -CH=CH-, and –O-."

4. Claim 18, 8th compound of page 28: "(1*,3R)-1-[4-(4-Fluorophenyl)$_4$-oxobutyl]-3-(2-hydroxy-2,2-dithien-2ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1);" should read "(1*,3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1);".

5. Paragraph [0008]: "B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl group or a 5 to 1-membered heteroaromatic group containing" should read "B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl group or a 5 to 10-membered heteroaromatic group containing".

6. Paragraph [0011]: "R^5 and R^8 each independently represent a hydrogen atom, " should read "R^5 and R^6 each independently represent a hydrogen atom, ".

7. Paragraph [0021]: "optionally substituted lower alkoxy, nitro, cyano, -CO_2R^2 or $-NR^2R^{13}$, wherein R^{12} and R^{13} are identical" should read "optionally substituted lower alkoxy, nitro, cyano, -CO_2R^{12} or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} are identical".

8. Paragraph [0041]: The fragment "6-(4-phenylbutoxy)hexyl, 4-phenoxybutyl, 4-(4-fluorophenyl)$_4$-oxobutyl or 4-oxo-4-phenylbutyl." at the end of the paragraph should read "6-(4-phenylbutoxy)hexyl, 4-phenoxybutyl, 4-(4-fluorophenyl)-4-oxobutyl or 4-oxo-4-phenylbutyl.".

9. Paragraph [0043]: The fragment "3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)$_4$-oxobutyl or 3-thien-2-ylpropyl." at the end of the paragraph should read "3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)-4-oxobutyl or 3-thien-2-ylpropyl.".

10. Paragraph [0088]: "1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)- -methylpyrrolidinium chloride" should read "1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride".

11. Paragraph [0091]: "3-{[(9-hydroxy-9H-fluoren-9-yl)carbonyl]oxy}-methyl-1-(4-oxo-4-phen- ylbutyl)pyrrolidinium formate" should read "3-{[(9-hydroxy-9H-fluoren-9-yl)carbonyl]oxy}-1-methyl-1-(4-oxo-4-phen-ylbutyl)pyrrolidinium formate".

12. Paragraph [0098]: "(3R)-3-2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide" should read "(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide".

13. Paragraph [0099]: "(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide" should read "(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide".

14. Paragraph [0100]: "(3S)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide" should read "(3S)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide".

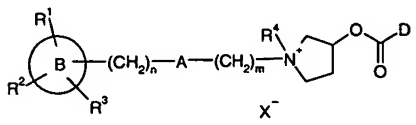
15. Paragraph [0132]: "(1*,3S)-3-[(2R)-2-Cyclopentyl-1-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)" should read "(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)".

16. Paragraph [0133]: "(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-methyl-1-(-3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)" should read "(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(-3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)".

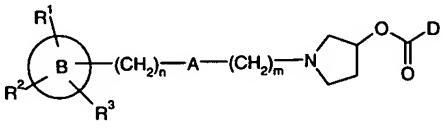
17. Paragraph [0149]: "(1*,3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2R)-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 1)" should read "(1*,3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 1)".

18. Paragraph [0152]: "(1*,3R-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyopyrrolidinium bromide (diastereomer 2)" should read "(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium bromide (diastereomer 2)".

19. Paragraph [0160]: formula (II) of the reaction pathway is erroneously depicted as



should be



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20. Paragraph [0455]: "(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo thien-2-ylbutyl)pyrrolidinium chloride" should read "(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo-4-thien-2-ylbutyl)pyrrolidinium chloride".

Correction and republication is respectfully requested.

Applicants believe that no Petition or fee is due in connection with this Request. However, if any Petition or fee is due, please grant the Petition and charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Respectfully submitted,

Dated: February 22, 2006

By: _____
Carlos M. Tellez
Reg. No. 48,638

Enclosures:
a) Marked-up copies of relevant pages of the published application (9 pages);
b) Corresponding pages of the originally filed application (13 pages); and
c) Relevant pages from the Preliminary Amendment filed on October 4, 2004 (4 pages).

PYRROLIDINIUM DERIVATIVES

[0001] This invention relates to new therapeutically useful pyrrolidinium derivatives, to some processes for their preparation and to pharmaceutical compositions containing them.

[0002] The novel structures according to the invention are antimuscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity for M3 muscarinic receptors. This subtype of muscarinic receptor is present in glands and smooth muscle and mediates the excitatory effects of the parasympathetic system on glandular secretion and on the contraction of visceral smooth muscle (Chapter 6, Cholinergic Transmission, in H. P. Rang et al., Pharmacology, Churchill Livingstone, N.Y., 1995).

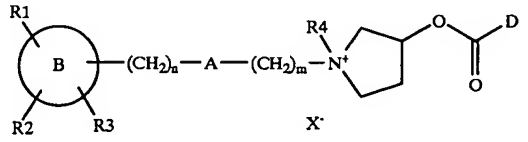
[0003] M3 antagonists are therefore known to be useful for treating diseases characterised by an increased parasympathetic tone, by excessive glandular secretion or by smooth muscle contraction (R. M. Eglen and S. S. Hegde, (1997), Drug News Perspect., 10(8):462-469).

[0004] Examples of this kind of diseases are respiratory disorders such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma, cough and rhinitis; urological disorders such as urinary incontinence, pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia (Chapter 7, Muscarinic Receptor Agonists and Antagonists, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edition, McGraw Hill, New York, 2001).

[0005] The compounds of the invention can be used alone or in association with other drugs commonly regarded as effective in the treatment of these diseases. For example, they can be administered in combination with β_2-agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors an/or leukotriene D4 (LTD4) antagonists for simultaneous, separate or sequential use in the treatment of a respiratory disease.

[0006] The new pyrrolidinium derivatives of the invention have the chemical structure of formula (I):

(I)



[0007] wherein

[0008] B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl group or a 5 to 1-membered heteroaromatic group containing one or more, for example 1, 2, 3 or 4, heteroatoms selected from N, O or S;

[0009] R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom, or a hydroxy, phenyl, $—OR^5$, $—SR^5$, $—NR^5R^6$, $—NHCOR^5$, $—CONR^5R^6$, —CN, $—NO_2$, $—COOR^5$ or $—CF_3$ group, or a straight or branched, optionally substituted lower alkyl group;

[0010] or R^1 and R^2 together form an aromatic or alicyclic ring or a heterocyclic group;

[0011] R^5 and R^6 each independently represent a hydrogen atom, a straight or branched, optionally substituted lower alkyl group, or together form an alicyclic ring;

[0012] n is an integer from 0 to 4;

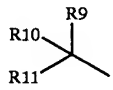
[0013] A represents a group selected from $—CH_2—$, $—CH=CR^7—$, $—CR^7=CH—$, $—CR^7R^8—$, —CO—, —O—, —S—, —S(O)—, $—S(O)_2—$ and $—NR^7—$, wherein R^7 and R^8 each independently represent a hydrogen atom, a straight or branched, optionally substituted lower alkyl group, or together form an alicyclic ring;

[0014] m is an integer from 0 to 8;

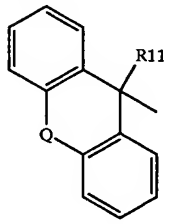
[0015] R^4 represents a lower alkyl group;

[0016] D represents a group of formula i) or ii)

i)



ii)



[0017] wherein

[0018] R^9 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl;

[0019] R^{10} represent a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl or C_3-C_7 cycloalkyl;

[0020] and R^{11} represents a hydrogen atom or a hydroxy, methyl, or $—CH_2OH$ group;

[0021] the cyclic groups represented by R^9 and R^{10} being optionally substituted by one or two substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, optionally substituted lower alkoxy, nitro, cyano, $—CO_2R^{12}$ or $—NR^{12}R^{13}$, wherein R^{12} and R^{13} are identical or different and are selected from hydrogen and straight or branched, optionally substituted lower alkyl groups;

[0022] Q represents a single bond or a $—CH_2—$, $—CH_2—CH_2—$, —O—, $—O—CH_2—$, —S—, $—S—CH_2—$ or —CH=CH— group;

[0023] X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

m- and p-tolyl, 3-cyanophenyl, 2-, 3- and 4-hydroxyphenyl and 2-, 3- and 4-fluorophenyl.

[0040] Preferred compounds of formula (I) are those wherein n=0 or 1; m is an integer from 1 to 6, particularly 1, 2 or 3; and A represents a —CH_2, —CH=CH—, —CO—, —NMe-, —O— or —S-group. Most preferred compounds are those wherein A is a —CH_2, —CH=CH— or —O— group.

[0041] Further preferred compounds of formula (I) are those wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 4-phenylbutyl, 3-phenylpropyl, 3-(2-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 2-benzyloxyethyl, 3-pyrrol-1-ylpropyl, 2-thien-2-ylethyl, 3-thien-2-ylpropyl, 3-phenylaminopropyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 3-tolyloxypropyl, 3-(2,4,6-trimethylphenoxy)propyl, 3-(2-tert-butyl-6-methylphenoxy)propyl, 3-(biphenyl-4-yloxy)propyl, 3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)-propyl, 3-(naphthalen-2-yloxy)propyl, 3-(naphthalen-1-yloxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(3-trifluoromethylphenoxy)propyl, 3-(3-cyanophenoxy)propyl, 3-(4-cyanophenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(4-methoxyphenoxy)propyl, 3-(benzo[1,3]dioxol-5-yloxy)propyl, 3-(2-carbamoylphenoxy)propyl, 3-(3-dimethylaminophenoxy)propyl, 3-(4-nitrophenoxy)propyl, 3-(3-nitrophenoxy)propyl, 3-(4-acetylaminophenoxy)propyl, 3-(4-methoxycarbonylphenoxy)propyl, 3-[4-(3-hydroxypropyl)phenoxy]propyl, 3-(2-hydroxymethylphenoxy)propyl, 3-(3-hydroxymethylphenoxy)propyl, 3-(4-hydroxymethylphenoxy)propyl, 3-(2-hydroxyphenoxy)propyl, 3-(4-hydroxyphenoxy)propyl, 3-(3-hydroxyphenoxy)propyl, 4-oxo-4-thien-2-ylbutyl, 3-(1-methyl-[1H]-imidazol-2-ylsulphanyl)propyl, 3-(benzothiazol-2-yloxy)propyl, 3-benzyloxypropyl, 6-(4-phenylbutoxy)hexyl, 4-phenoxybutyl, 4-(4-fluorophenyl)-4-oxobutyl or 4-oxo-4-phenylbutyl.

[0042] Most preferred are those compounds wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl , 3-thien-2-ylpropyl, 4-oxo-4-thien-2-ylbutyl, 2-benzyloxyethyl, 3-o-tolyloxypropyl, 3-(3-cyanophenoxy)propyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 4-oxo-4-phenylbutyl, 4-(4-fluorophenyl)-4-oxobutyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(4-methoxyphenoxy)propyl, 3-(benzo[1,3]dioxol-5-yloxy)propyl.

[0043] Examples of especially preferred compounds are those wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)-4-oxobutyl or 3-thien-2-ylpropyl.

[0044] Further preferred compounds of formula (I) are those wherein D is a group of formula i), and wherein R^9 is a group selected from phenyl, 2-thienyl, 3-thienyl, 3-furyl or 2-furyl more preferably phenyl, 2-thienyl or 2-furyl; R^{10} is a group selected from phenyl, 2-thienyl, 2-furyl, 3-furyl, 3-thienyl, cyclohexyl or cyclopentyl more preferably phenyl, 2-thienyl, cyclohexyl or cyclopentyl; and R^{11} is a hydroxy group.

[0045] Also preferred are compounds of formula (I) wherein D is a group of formula ii), and wherein Q is a single bond or an oxygen atom and R^{11} is a hydrogen atom or a hydroxy group.

[0046] The compounds of the present invention represented by formula (I) have at least two chiral centers: one at the carbon atom in position 3 of the pyrrolidinium ring and another at the N atom of the pyrrolidinium ring. Additionally, depending on the nature of group D they may also have an additional chiral center at the carbon atom of this group which is attached to the ester function. Each of these chiral centers may have R- or S-configuration. The single isomers and mixtures of the isomers fall within the scope of the invention.

[0047] Since the compounds have one or more chiral centers they may be obtained as pure isomers or as mixtures of the different enantioners or diastereomers.

[0048] In the present invention when no indication is given on the configuration of a chiral center, it is to be understood that reference is made to the mixture of all posible isomers at the corresponding chiral center.

[0049] When compounds with a specific configuration at a chiral center are meant, this is indicated in the name of the compound as follows:

[0050] when the configuration at the chiral center is known, it is indicated by using the Cahn-Ingold-Prelog nomenclature attaching the letter R or S to the number specifying the position of the chiral center in the molecule.

[0051] when the chiral center has a specific configuration which is however unknown, it is indicated by attaching an asterisc (*) to the number specifying the position of the chiral center in the molecule.

[0052] Particular compounds of the invention include:

[0053] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium trifluoroacetate

[0054] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide

[0055] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide

[0056] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl) pyrrolidinium bromide

[0057] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium trifluoroacetate

[0058] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo-4-thien-2-ylbutyl)pyrrolidinium trifluoroacetate

[0059] 1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium trifluoroacetate

[0060] 1-Ethyl-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]pyrrolidinium trifluoroacetate

[0061] 3-(2-Hydroxy-2,2-dithien-2-yl-acetoxy)-1-methyl-1-(3-pyrrol-1-ylpropyl)pyrrolidinium trifluoroacetate

[0062] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-[6-(4-phenylbutoxy)hexyl]pyrrolidinium trifluoroacetate

[0063] 1-(2-Benzyloxyethyl)-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate

[0064] 1-[3-(3-Cyanophenoxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate

[0065] 3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(naphthalen-1-yloxy)propyl]pyrrolidinium trifluoroacetate

[0066] 3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(methylphenylamino)propyl]pyrrolidinium trifluoroacetate

[0067] 3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate

[0068] 1-[3-(Benzothiazol-2-yloxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate

[0069] 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

[0070] 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(2,4,6-trimethylphenoxy)propyl]pyrrolidinium trifluoroacetate

[0071] 1-[3-(2-Chlorophenoxy)propyl]-3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxyl-1-methylpyrrolidinium trifluoroacetate

[0072] 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(3-trifluoromethylphenoxy)propyl]pyrrolidinium trifluoroacetate

[0073] 1-[3-(Biphenyl-4-yloxy)propyl]-3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methylpyrrolidinium trifluoroacetate

[0074] 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-[3-(2,4-difluorophenoxy)propyl]-1-methylpyrrolidinium trifluoroacetate

[0075] 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-ethyl-1-[3-(4 methoxyphenoxy)propyl]pyrrolidinium trifluoroacetate

[0076] 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(5,6,7,8 tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium trifluoroacetate

[0077] 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(1-methyl-1H-imidazol-2-ylsulphanyl-)propyl]pyrrolidinium trifluoroacetate

[0078] 1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

[0079] 1-Methyl-1-(3-phenoxypropyl)-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

[0080] 1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

[0081] 1-[3-(2-Carbamoylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

[0082] 1-[3-(3-Dimethylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

[0083] 1-[3-(4-Acetylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

[0084] 1-[3-(4-Methoxycarbonylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

[0085] 1-Methyl-1-[3-(4-nitrophenoxy)propyl]-3 (9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

[0086] 1-[3-(4-Hydroxymethylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

[0087] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-methylpyrrolidinium formate 2-ylacetoxy)-1-methylpyrrolidinium

[0088] 1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-methylpyrrolidinium chloride

[0089] 3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide

[0090] 1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide

[0091] 3-{[(9-hydroxy-9H-fluoren-9-yl)carbonyl]oxy}-1-(4-oxo-4-phenylbutyl)pyrrolidinium formate carbonyl]oxy}-1-methyl

[0092] 3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-ethyl-1-(3-phenylsulfanylpropyl)pyrrolidinium bromide

[0093] Particular mixtures of isomers of the compounds of the invention include:

[0094] (3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide

[0095] (3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide

[0096] (3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide

[0097] (3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide

[0098] (3R)-3-2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide [3R)-3-(2-Hydroxy

[0099] (3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide ylacetoxy)-1-methyl

[0100] (3S)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

[0101] (3R)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate

[0102] (3S)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate

[0103] (3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

[0104] (3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

[0105] (3R)-3-[(2S-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

[0106] (3S)-3-[(2S-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

[0107] (3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

[0108] (3S)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

[0109] (3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-methylpyrrolidinium formate

[0110] (3R)-3-{[(9-hydroxy-9H-fluoren-9-yl)carbonyl]oxy}1-methyl-1-(4-oxo-4-phenylbutyl)pyrrolidinium formate

[0111] (3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo-4-thien-2-ylbutyl)pyrrolidinium chloride

[0112] (3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium formate

[0113] (3R)-1-[3-(3-Cyanophenoxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium formate

[0114] (3R)-3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(naphthalen-1-yloxy)propyl]pyrrolidinium formate

[0115] (3R)-3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(methylphenylamino)propyl] pyrrolidinium chloride

[0116] (3R)-1-[3-(Benzothiazol-2-yloxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium chloride

[0117] (3R)-1-[3-(Biphenylyloxy)propyl]-3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride

[0118] (3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium bromide

[0119] (3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(1-methyl-1H-imidazol-2-ylsulfanyl)propyl]pyrrolidinium chloride

[0120] (3R)-1-[3-(2-Chlorophenoxy)propyl]-3-[(2R-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride

[0121] 3-[(2R-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-ethyl-1-[3-(4-methoxyphenoxy)propyl]pyrrolidinium bromide

[0122] (3R)-1-(2-Benzyloxyethyl)-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium bromide

[0123] Individual isomers of the compounds of the invention include:

[0124] (1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide (diastereomer 1)

[0125] (1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy-1-methyl-1-phenethylpyrrolidinium bromide (diastereomer 2)

[0126] (1*,3R-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereomer 1)

[0127] (1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereomer 2)

[0128] (1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereomer 1)

[0129] (1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereomer 2)

[0130] (1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

[0131] (1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2) Cyclopentyl-2-hydroxy

[0132] (1*,3S)-3-[(2R)-2-Cyclopentyl-1-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

[0133] (1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2) phenyl acetoxy]-1-methyl

[0134] (1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 1)

[0135] (1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 2)

[0136] (1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 1)

[0137] (1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 2)

[0138] (1*,3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

[0139] (1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

[0140] (1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 2)

[0141] (1*,3S-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 1)

[0142] (1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 2)

[0143] (1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

[0144] (1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)

[0145] (1*,3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1)

[0146] (1*,3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2)

[0147] (1*,3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1)

[0148] (1*,3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2)

[0149] (1*,3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2R)-cyclopentyl]2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 1).

[0150] (1*,3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 2).

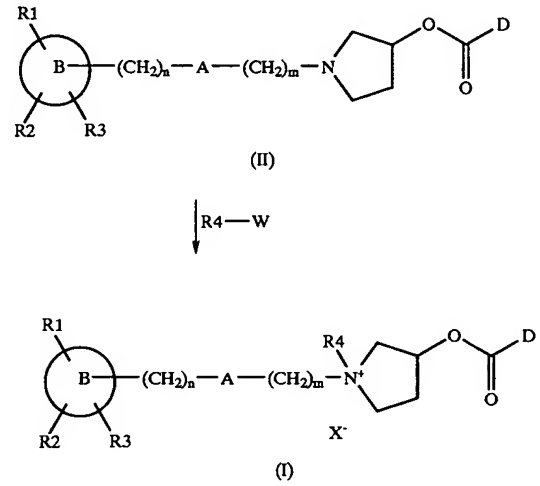
[0151] (1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium bromide (diastereomer 1).

[0152] (1*,3R-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyopyrrolidinium bromide (diastereomer 2).

[0153] In accordance with another embodiment, the present invention provides processes for preparing the novel pyrrolidinium derivatives of formula (I). These compounds may be prepared following two different procedures, illustrated below as method (a) and method (b).

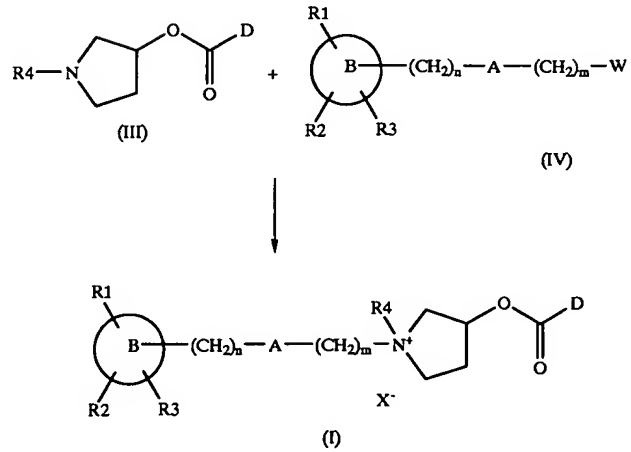
[0154] Following method (a), the compounds of formula (I) are obtained by reaction of an alkylating agent of formula R4-W with intermediates of formula (II).

Method a



[0155] Following method (b) the compounds of formula (I) are prepared by reaction of an alkylating agent of formula (IV) with intermediates of formula (III).

Method b



[0156] In formulae (I), (II), (III) and (IV), m, n, A, B, D, R1, R2, R3 and R4 and X^- are as defined above.

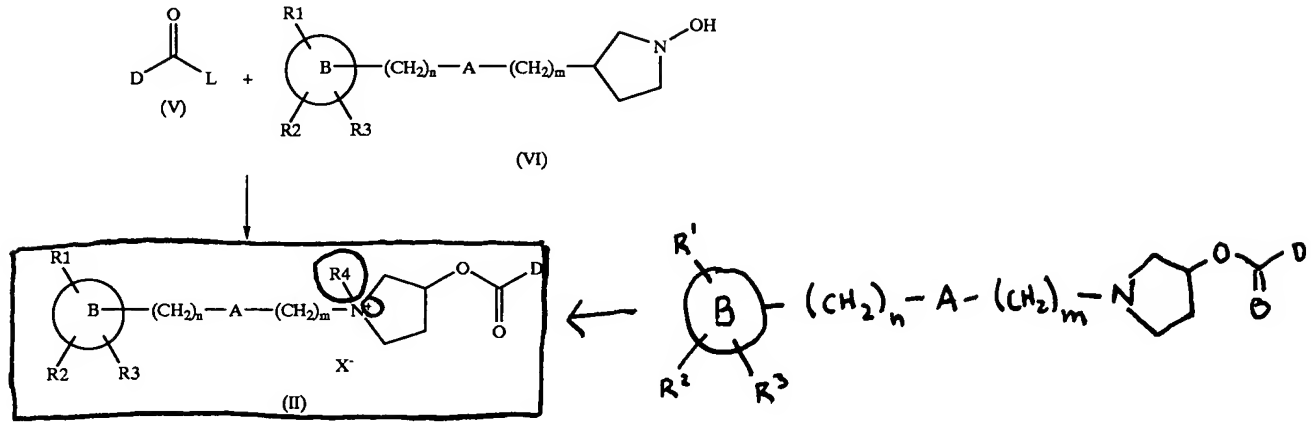
[0157] In formulae (IV) and R4-W, W represents any suitable leaving group, such a group X as defined above for the compounds of formula (I). Preferably, W represents a group X. When W represents a group other than X, the quaternary ammonium salt of formula (I) is produced from the product of method (a) or (b) by an exchange reaction according to standard methods to replace the anion W^- with the desired anion X^-.

[0158] Methods (a) and (b) may be carried out by known experimental procedures in conventional synthesis, or using solid phase extraction methodologies, which allow the parallel preparation of several compounds .

[0159] The diastereomers of compounds of formula (I) may be separated by conventional methods, for example by chromatography or crystallisation.

[0160] The intermediates of formula (II) used in method (a) may be prepared by reaction of a compound of formula (V) with a compound of formula (VI) as shown in method (c) below

Method c



[0161] In formulae (II), (V) and (VI), m, n, A, B, D, R1, R2 and R3 are as defined above.

[0162] The pyrrolidinol esters of formula (II) may be converted to pharmaceutically acceptable salts by methods known in the art. Typically, an ester of formula (II) is treated with an inorganic or organic acid such as oxalic, fumaric, maleic, tartaric, succinic or hydrochloric acid.

[0163] The pyrrolidinol esters of formula (II) having one or more asymmetric carbons, include all the possible stereoisomers, single isomers and mixtures of isomers.

[0164] The diastereomers of compounds of formula (II) may be separated by conventional methods, for example by chromatography or crystallisation. Certain compounds of formula (II) are novel and fall under the scope of the present invention. In particular

[0165] 2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester

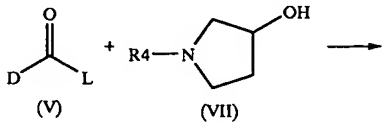
[0166] 2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester

[0167] 2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester

[0168] 2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-phenethylpyrrolidin-3-yl ester

[0169] The compounds of formula (III), used in method (b), may be prepared by reaction of a compound of formula (V) with a compound of formula (VII) as described in method (d), illustrated below.

Method d



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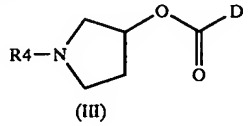


[0170] In the compounds of formulae (V), (III), and (VII), D and R4 are as described above for compounds of formula (I); and L in formula (V) represents a leaving group. For example, L may be a chlorine atom, an imidazol-1-yl group or a lower alkoxy group, such as a methoxy group.

[0171] The intermediates of formula (V) may be prepared by methods described in the literature as shown in the experimental section below.

[0172] The pyrrolidinol esters of formula (III) having one or more asymmetric carbons, include all the possible stere-

[0453] ^{1}H-NMR (DMSO-d_6): δ 7.58-7.49 (m, 5H), 7.45-7.36 (m, 3H), 7.18 (dd, 1H), 7.13 (dd, 1H), 7.02-6.97 (m, 2H), 6.80 (d, 1H), 6.51-6.39 (m, 1H), 5.56 (m, 1H), 4.05 (d, 2H), 3.93-3.72 (m, 3H), 3.64-3.53 (m, 1H), 3.13 (s, 3H), 2.80-2.71 (m, 1H), 2.24-2.13 (m, 1H).

[0454] MS [M-Br]$^+$: 440

[0455] (* Configuration not assigned)

EXAMPLE 15

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo thien-2-ylbutyl)pyrrolidinium chloride

[0456] The title compound was obtained as a mixture of two stereoisomers according to method (b) from Intermediate I-5.

[0457] The reaction time for the final step (conditions: THF, reflux temperature) was 7 days. Purification of the product by several washings with THF at reflux temperature, gave 120 mg (8%) of the title compound (mixture of two stereoisomers).

[0458] HPLC: mixture of diastereomers 38:62

[0459] ^{1}H-NMR (DMSO-d_6): δ 8.06-7.98 (m, 2H), 7.60 (s, OH, 1H), 7.52-7.45 (m, 2H), 7.30-7.25 (m, 1H), 7.18-7.11 (m, 2H), 7.02-6.95 (m, 2H), 5.51 (m, 1H), 4.02-3.00 (m, 8H), 3.15 and 3.00 (s, 3H), 2.78-2.65 (m, 1H), 2.23-1.96 (m, 3H).

[0460] MS [M-Cl]$^+$: 476.

EXAMPLE 16

(1*,3R)-1-[4-4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

[0461] The title compound was obtained as a single isomer according to method (b) from Intermediate I-5.

[0462] The reaction time for the final step (conditions: THF, reflux temperature) was 13 days. Purification by column chromatography (silica gel, eluent: $CHCl_3$ plus isopropanol 10%→90%) gave 187 mg (25%) of the title compound (only eluted diastereomer).

[0463] ^{1}H-NMR: diastereomer 1

[0464] ^{1}H-NMR (DMSO-d_6): δ 8.10-8.04 (m, 2H), 7.55-7.51 (m, 3H), 7.38 (t, 2H), 7.18-7.13 (m, 2H), 7.03-6.99 (m, 2H), 5.53 (m, 1H), 3.95-3.70 (m, 3H), 3.65-3.35 (m, 3H), 3.16 (m, 2H), 2.99 (s, 3H), 2.79-2.64 (m, 1H), 2.22-2.02 (m, 3H).

[0465] MS [M-Cl]$^+$: 488

[0466] (* Configuration not assigned)

EXAMPLE 17

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

[0467] The title compound was obtained as a single isomer according to method (b) from Intermediate I-6.

[0468] The reaction time for the final step (conditions: THF, reflux temperature) was 11 days. Purification by column chromatography (silica gel, eluent: $CHCl_3$ plus isopropanol 10%→85%) gave 309 mg-(41.5%) of the title compound (first eluted diastereomer).

[0469] ^{1}H-NMR: diastereomer 1 (diastereomer 2 not observed)

[0470] ^{1}H-NMR (DMSO-d_6): δ 7.54-7.51 (m, 3H), 7.17-7.11 (m, 4H), 7.03-6.93 (m, 4H), 5.53 (m, 1H), 4.02 (t, 2H), 3.95-3.38 (m, 6H), 2.98 (s, 3H), 2.80-2.67 (m, 1H), 2.24-2.12 (m, 3H).

[0471] MS [M-Cl]$^+$: 476.

[0472] (* Configuration not assigned)

EXAMPLE 18

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 2)

[0473] The title compound was obtained as a single isomer according to method (b) from Intermediate I-6.

[0474] The reaction time for the final step (conditions: THF, reflux temperature) was 11 days. Purification by column chromatography (silica gel, eluent: $CHCl_3$ plus isopropanol 10%→85%) gave 62 mg (8.5%) of the title compound (second eluted diastereomer).

[0475] ^{1}H-NMR: diastereomer 2 (diastereomer 1 not observed).

[0476] ^{1}H-NMR (DMSO-d_6): δ 7.49-7.47 (m, 3H), 7.19-7.10 (m, 4H), 6.99-6.92 (m, 4H), 5.54 (m, 1H), 3.98-3.88 (m, 3H), 3.75-3.61 (m, 3H), 3.50-3.40 (m, 2H), 3.14 (s, 3H), 2.79-2.64 (m, 1H), 2.23-2.06 (m, 3H).

[0477] MS [M-Cl]$^+$: 476.

[0478] (* Configuration not assigned)

EXAMPLE 19

(1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 1)

[0479] The title compound was obtained as a single isomer according to method (b) from Intermediate I-6.

[0480] The reaction time for the final step (conditions: THF, reflux temperature) was 8 days.

[0481] Purification by column chromatography (silica gel, eluent: $CHCl_3$ plus isopropanol 10%→60%) gave 250 mg (31.2%) of the title compound (first eluted diastereomer).

[0482] ^{1}H-NMR: diastereomer 1 (diastereomer 2 not observed).

[0483] ^{1}H-NMR (DMSO-d_6): δ 7.46-7.44 (m, 3H), 7.29-7.13 (m, 5H), 7.10-7.05 (m, 2H), 6.96-6.92 (m, 2H), 5.45 (m, 1H), 3.85-3.77 (m, 1H), 3.71-3.31 (m, 5H), 2.87 (s, 3H), 2.71-2.58 (m, 1H), 2.54 (t, 2H), 2.13-1.90 (m, 3H).

[0484] MS [M-Br]$^+$: 442

[0485] (* Configuration not assigned)

or R^1 and R^2 together form an aromatic or alicyclic ring or a heterocyclic group;

R^5 and R^6 each independently represent a group chosen from a hydrogen atom, a straight optionally substituted lower alkyl group and a branched optionally substituted lower alkyl group, or R^5 and R^6 together form an alicyclic ring;

n is an integer from 0 to 4;

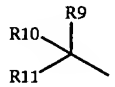
A represents a group chosen from $—CH_2—$, $—CH=CR^7—$, $—CR^7=CH—$, $—CR^7R^8—$, —CO—, —O—, —S—, —S(O)—, $—S(O)_2—$ and $—NR^7—$, wherein R^7 and R^8 each independently represent a group chosen from hydrogen atom, a straight optionally substituted lower alkyl group and a branched optionally substituted lower alkyl group, or R^7 and R^8 together form an alicyclic ring;

m is an integer from 0 to 8;

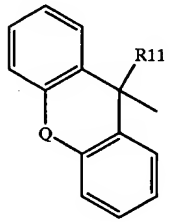
R^4 represents a lower alkyl group;

D represents a group of formula i) or ii)

i)



ii)



wherein

R^9 represents a group chosen from phenyl, 2-furyl, 3-furyl, 2-thienyl and 3-thienyl;

R^{10} represents a group chosen from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl and C_3-C_7 cycloalkyl;

and R^{11} represents a group chosen from a hydrogen atom, hydroxy, methyl, and CH_2OH;

wherein each of the cyclic groups represented by R^9 and R^{10} independently optionally substituted by one or two substituents chosen from halogen, straight optionally substituted lower alkyl, branched optionally substituted lower alkyl, hydroxy, optionally substituted lower alkoxy, nitro, cyano, $—CO_2R^{12}$ and $—NR^{12}R^{13}$, wherein R^{12} and R^{13} are identical or different and are each independently chosen from a hydrogen atom, straight optionally substituted lower alkyl groups and branched optionally substituted lower alkyl groups;

Q represents a single bond or a group chosen from $—CH_2—$, $—CH_2—CH_2—$, —O—, $—O—CH_2—$, —S—, $—S—CH_2—$ and —CH=CH—

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

or an individual stereoisomers of a compound of formula (I) or mixture of stereoisomers of a compound of formula (I);

with the proviso that in those compounds of formula (I) wherein B is phenyl, R^9 is unsubstituted phenyl, R^{10} is unsubstitued phenyl or unsubstituted C_3-C_7 cycloalkyl, and R^{11} is hydrogen or hydroxy, the sequence $—(CH_2)_n$-A-$(CH_2)_m—$ is not one of methylene, ethylene or propylene.

2. A compound according to claim 1, wherein B represents a group chosen from phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl and benzothiazolyl.

3. A compound according to claim 2, wherein B represents a group chosen from phenyl, thienyl and pyrrolyl.

4. A compound according to claim 1, wherein R^1, R^2 and R^3 each independently represents a group chosen from a hydrogen atom, a halogen atom, hydroxy, methyl, tert-butyl, $—CH_2OH$, 3-hydroxypropyl, —OMe, $—NMe_2$, —NHCOMe, $—CONH_2$, —CN, $—NO_2$, —COOMe and $—CF_3$.

5. A compound according to claim 4, wherein R1, R^2 and R^3 each independently represents a group chosen from hydrogen, fluorine, chlorine and hydroxy.

6. A compound according to claim 1, wherein n=0 or 1; m is an integer from 1 to 6; and A represents a group chosen from $—CH_2—$, —CH=CH—, —CO—, —NMe-, —O— and —S—.

7. A compound according to claim 6, wherein A is a group chosen from $—CH_2—$, —CH=CH— and —O—

8. A compound according to claim 6, wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group chosen from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thien-2-ylpropyl, 4-oxo-4-thien-2-ylbutyl, 2-benzyloxyethyl, 3-o-tolyloxypropyl, 3-(3-cyanophenoxy)propyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 4-oxo-4-phenylbutyl, 4-(4-fluorophenyl)-4-oxobutyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(4-methoxyphenoxy)propyl, and 3-(benzo[1,3]dioxol-5-yloxy)propyl.

9. A compound according to claim 8 wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group chosen from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)-4-oxobutyl and 3-thien-2-ylpropyl.

10. A compound according to claim 1, wherein D is a group of formula i), and wherein R^9 is a group chosen from phenyl, 2-thienyl and 2-furyl; R^{10} is a group chosen from phenyl, 2-thienyl, cyclohexyl and cyclopentyl; and R^{11} is a hydroxy group.

11. A compound according to claim 1, wherein D is a group of formula ii), and wherein Q is a single bond or an oxygen atom and R^{11} is a hydrogen atom or a hydroxy group.

12. A compound according to claim 1, wherein X^- is chosen from chloride, bromide, trifluoroacetate sand methanesulphonate.

13. A compound according to claim 1, wherein the carbon at the 3-position of the pyrrolidinium ring has a R configuration.

(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2);

(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1);

(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2);

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 1);

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 2);

(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 1);

(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 2);

(1*,3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1);

[4-(4-Fluorophenyl)-4-oxobutyl]

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1);

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 2);

(1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 1);

(1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 2);

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1);

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2);

(1*,3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1);

(1*,3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2);

(1*,3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1);

(1*,3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2);

(1*,3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 1);

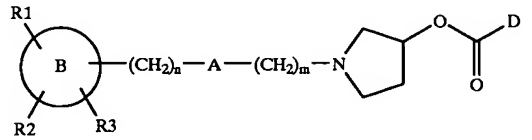
(1*,3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 2);

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium bromide (diastereomer 1); and

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium bromide (diastereomer 2).

21. A process for producing a compound of formula (I), as claimed in claim 1, comprising reacting an alkylating agent of formula R4-W with an intermediate of formula (II)

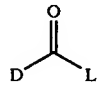
(II)



wherein W is a leaving group.

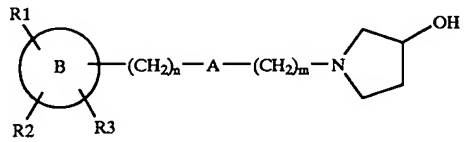
22. A process according to claim 21, wherein the compound of formula (II) is obtained by reaction of a compound of formula (V)

(V)



wherein L is a leaving group, with a compound of formula (VI)

(VI)



23. A compound chosen from:

2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester;

2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester;

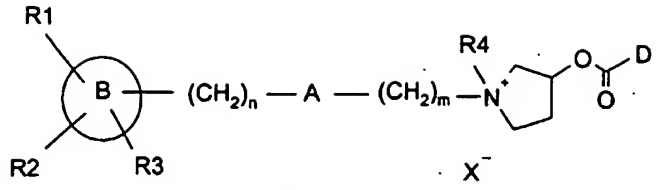
2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester; and

2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-phenethylpyrrolidin-3-yl ester.

24. A compound chosen from:

(3R)-1-(3-phenoxypropyl)pyrrolidin-3-ol and

(3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-ol.



(I)

wherein

B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl group or a 5 to 10-membered heteroaromatic group containing one or more, for example 1, 2, 3 or 4, heteroatoms selected from N, O or S;

FOR PARAGRAPH [0008] OF PUBLISHED APPLICATION

R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom, or a hydroxy, phenyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-NHCOR^5$, $-CONR^5R^6$, -CN, $-NO_2$, $-COOR^5$ or $-CF_3$ group, or a straight or branched, optionally substituted lower alkyl group;

or R^1 and R^2 together form an aromatic or alicyclic ring or a heterocyclic group;

R^5 and R^6 each independently represent a hydrogen atom, a straight or branched, optionally substituted lower alkyl group, or together form an alicyclic ring;

FOR CA [0011]

n is an integer from 0 to 4;

A represents a group selected from $-CH_2-$, $-CH=CR^7-$, $-CR^7=CH-$, $-CR^7R^8-$, -CO-, -O-, -S-, -S(O)-, $-S(O)_2-$ and $-NR^7-$, wherein R^7 and R^8 each independently represent a hydrogen atom, a straight or branched, optionally substituted lower alkyl group, or together form an alicyclic ring;

m is an integer from 0 to 8;

R^4 represents a lower alkyl group;

D represents a group of formula i) or ii)

i) ii)

wherein

R^9 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl;

R^{10} represent a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl or C_3-C_7 cycloalkyl;

and R^{11} represents a hydrogen atom or a hydroxy, methyl, or $-CH_2OH$ group;

the cyclic groups represented by R^9 and R^{10} being optionally substituted by one or two substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, optionally substituted lower alkoxy, nitro, cyano, $-CO_2R^{12}$ or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} are identical or different and are selected from hydrogen and straight or branched, optionally substituted lower alkyl groups;

For a Cooz

Q represents a single bond or a $-CH_2-$, $-CH_2-CH_2-$, -O-, $-O-CH_2-$, -S-, $-S-CH_2-$ or -CH=CH- group;

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

including all individual stereoisomers and mixtures thereof

with the proviso that in those compounds wherein B is phenyl, R^9 is unsubstituted phenyl, R^{10} is unsubstitued phenyl or unsubstituted C_3-C_7 cycloalkyl, R^{11} is hydrogen or hydroxy, the sequence $-(CH_2)_n-A-(CH_2)_m-$ is not one of methylene, ethylene or propylene.

Further objectives of the present invention are to provide processes for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the

3-(2-hydroxymethylphenoxy)propyl, 3-(3-hydroxymethylphenoxy)propyl, 3-(4-hydroxymethylphenoxy)propyl, 3-(2-hydroxyphenoxy)propyl, 3-(4-hydroxyphenoxy)propyl, 3-(3-hydroxyphenoxy)propyl, 4-oxo-4-thien-2-ylbutyl, 3-(1-methyl-[1H]-imidazol-2-ylsulphanyl)propyl, 3-(benzothiazol-2-yloxy)propyl, 3-benzyloxypropyl, 6-(4-phenylbutoxy)hexyl, 4-phenoxybutyl, 4-(4-fluorophenyl)-4-oxobutyl or 4-oxo-4-phenylbutyl.

For ¶ [0041]

Most preferred are those compounds wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl , 3-thien-2-ylpropyl, 4-oxo-4-thien-2-ylbutyl, 2-benzyloxyethyl, 3-o-tolyloxypropyl, 3-(3-cyanophenoxy)propyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 4-oxo-4-phenylbutyl, 4-(4-fluorophenyl)-4-oxobutyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(4-methoxyphenoxy)propyl, 3-(benzo[1,3]dioxol-5-yloxy)propyl.

Examples of especially preferred compounds are those wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)-4-oxobutyl or 3-thien-2-ylpropyl.

For ¶ [0043]

Further preferred compounds of formula (I) are those wherein D is a group of formula i), and wherein R^9 is a group selected from phenyl, 2-thienyl, 3-thienyl, 3-furyl or 2-furyl more preferably phenyl, 2-thienyl or 2-furyl; R^{10} is a group selected from phenyl, 2-thienyl, 2-furyl, 3-furyl, 3-thienyl, cyclohexyl or cyclopentyl more preferably phenyl, 2-thienyl, cyclohexyl or cyclopentyl; and R^{11} is a hydroxy group.

Also preferred are compounds of formula (I) wherein D is a group of formula ii), and wherein Q is a single bond or an oxygen atom and R^{11} is a hydrogen atom or a hydroxy group.

3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium trifluoroacetate

3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(1-methyl-1H-imidazol-2-ylsulphanyl)propyl]pyrrolidinium trifluoroacetate

1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

1-Methyl-1-(3-phenoxypropyl)-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

1-[3-(2-Carbamoylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

1-[3-(3-Dimethylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

1-[3-(4-Acetylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

1-[3-(4-Methoxycarbonylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

1-Methyl-1-[3-(4-nitrophenoxy)propyl]-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

1-[3-(4-Hydroxymethylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-methylpyrrolidinium formate

1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride

FOR ¶ [0088]

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide

1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide

3-{[(9-hydroxy-9H-fluoren-9-yl)carbonyl]oxy}-1-methyl-1-(4-oxo-4-phenylbutyl)pyrrolidinium formate

FOR ¶ [0091]

3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-ethyl-1-(3-phenylsulfanylpropyl)pyrrolidinium bromide

Particular mixtures of isomers of the compounds of the invention include:

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide

(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide

(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

(3R)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate

(3S)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate

(3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

(3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

(3R)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

(3S)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

(3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

(3S)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide

(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-methylpyrrolidinium formate

(3R)-3-[[(9-hydroxy-9H-fluoren-9-yl)carbonyl]oxy]-1-methyl-1-(4-oxo-4-phenylbutyl)pyrrolidinium formate

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo-4-thien-2-ylbutyl)pyrrolidinium chloride

(3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium formate

(3R)-1-[3-(3-Cyanophenoxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium formate

(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)

(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 1)

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 2)

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 1)

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 2)

(1*, 3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 2)

(1*, 3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 1)

(1*, 3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 2)

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)

(1*, 3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1)

(1*, 3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2)

(1*, 3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1)

(1*, 3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-

[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2)

(1*, 3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 1).

(1*, 3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methylpyrrolidinium chloride (diastereomer 2).

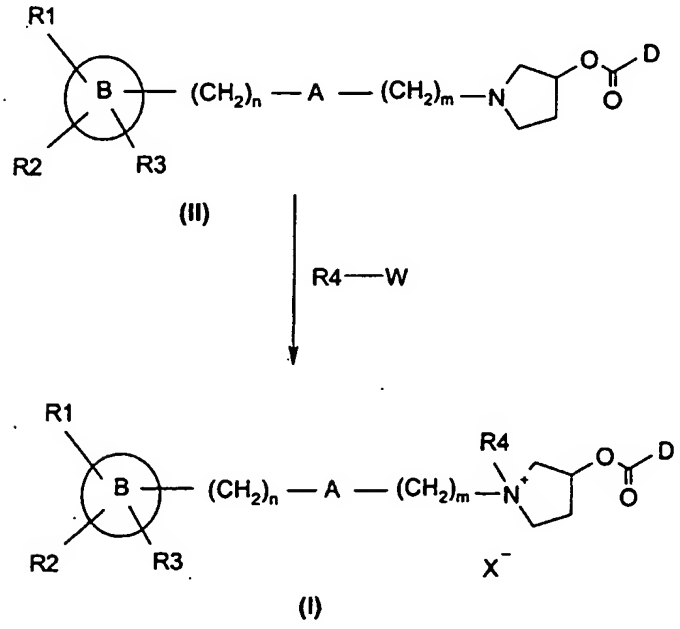
(1*, 3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium bromide (diastereomer 1).

(1*, 3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium bromide (diastereomer 2).

In accordance with another embodiment, the present invention provides processes for preparing the novel pyrrolidinium derivatives of formula (I). These compounds may be prepared following two different procedures, illustrated below as method (a) and method (b).

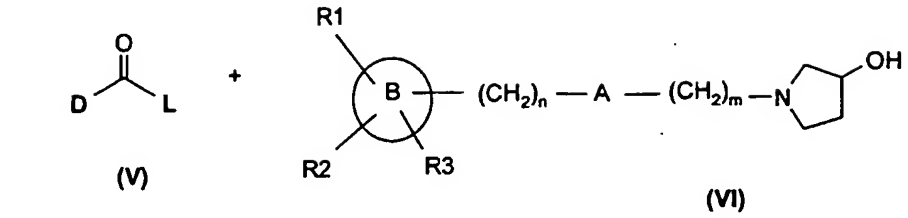
Following method (a), the compounds of formula (I) are obtained by reaction of an alkylating agent of formula R4-W with intermediates of formula (II).

Method a

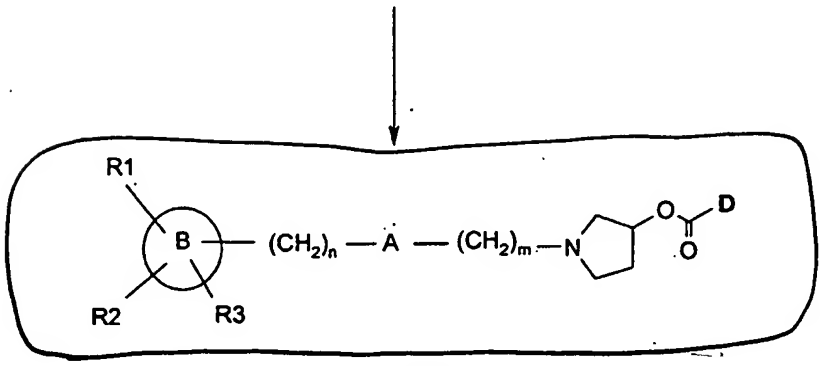


Following method (b) the compounds of formula (I) are prepared by reaction of an alkylating agent of formula (IV) with intermediates of formula (III) .

Method c



(V) (VI)



(II)

FOR 9A [0160]

In formulae (II), (V) and (VI), m, n, A, B, D, R1, R2 and R3 are as defined above.

The pyrrolidinol esters of formula (II) may be converted to pharmaceutically acceptable salts by methods known in the art. Typically, an ester of formula (II) is treated with an inorganic or organic acid such as oxalic, fumaric, maleic, tartaric, succinic or hydrochloric acid.

The pyrrolidinol esters of formula (II) having one or more asymmetric carbons, include all the possible stereoisomers, single isomers and mixtures of isomers.

The diastereomers of compounds of formula (II) may be separated by conventional methods, for example by chromatography or crystallisation. Certain compounds of formula (II) are novel and fall under the scope of the present invention. In particular:

2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester
2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester
2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester
2-Hydroxy-2,2-dithien-2-ylacetic acid (3R)-1- phenethylpyrrolidin-3-yl ester

Example 13

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 1)

The title compound was obtained as a single isomer according to method (b) from Intermediate I-5.

The reaction time for the final step (conditions: THF, reflux temperature) was 2 h. Purification by column chromatography (silica gel, eluent: CH_2Cl_2 plus isopropanol 30%→80%) gave 358 mg (44.2%) of the title compound (first eluted diastereomer).

^{1}H-NMR: diastereomer 1 (diastereomer 2 not observed)

^{1}H-NMR (DMSO-d_6): δ 7.60 - 7.50 (m, 5H), 7.44 - 7.34 (m, 3H), 7.16 - 7.12 (m, 2H), 7.02 - 6.98 (m, 2H), 6.91 (d, 1H), 6.57 - 6.45 (m, 1H), 5.55 (m, 1H), 4.24 (d, 2H), 4.04 - 3.96 (m, 1H), 3.74 - 3.64 (m, 3H), 2.97 (s, 3H), 2.79 - 2.67 (m, 1H), 2.23 - 2.12 (m, 1H).

MS $[M-Br]^+$: 440

(* Configuration not assigned)

Example 14

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 2)

The title compound was obtained as a single isomer according to method (b) from Intermediate I-5.

The reaction time for the final step (conditions: THF, reflux temperature) was 2 h. Purification by column chromatography (silica gel, eluent: CH_2Cl_2 plus isopropanol 30%→80%) gave 160 mg (19.8%) of the title compound (second eluted diastereomer).

^{1}H-NMR: diastereomer 2 (diastereomer 1 not observed)

^{1}H-NMR (DMSO-d_6) : δ 7.58 - 7.49 (m, 5H), 7.45 - 7.36 (m, 3H), 7.18 (dd, 1H), 7.13 (dd, 1H), 7.02 - 6.97 (m, 2H), 6.80 (d, 1H), 6.51 - 6.39 (m, 1H), 5.56 (m, 1H), 4.05 (d, 2H), 3.93 - 3.72 (m, 3H), 3.64 - 3.53 (m, 1H), 3.13 (s, 3H), 2.80 - 2.71 (m, 1H), 2.24 - 2.13 (m, 1H).

MS $[M-Br]^+$: 440

(* Configuration not assigned)

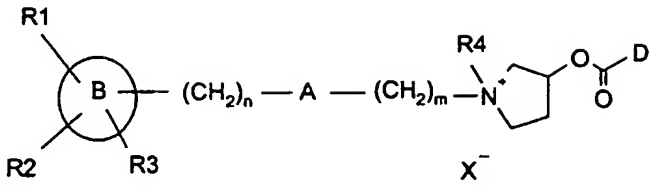
FOR Example 15 title under ¶ [0455]

Example 15

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo-4-thien-2-ylbutyl)pyrrolidinium chloride

CLAIMS

1. A compound of formula (I):



(I)

wherein

B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl group or a 5 to 10-membered heteroaromatic group containing one or more heteroatoms selected from N, O or S;

R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom, or a hydroxy, phenyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-NHCOR^5$, $-CONR^5R^6$, -CN, $-NO_2$, $-COOR^5$ or $-CF_3$ group, or a straight or branched, optionally substituted lower alkyl group;

or R^1 and R^2 together form an aromatic or alicyclic ring or a heterocyclic group;

R^5 and R^6 each independently represent a hydrogen atom, a straight or branched, optionally substituted lower alkyl group, or together form an alicyclic ring;

n is an integer from 0 to 4;

A represents a group selected from $-CH_2-$, $-CH=CR^7-$, $-CR^7=CH-$, $-CR^7R^8-$, -CO-, -O-, -S-, -S(O)-, $-S(O)_2-$ and $-NR^7-$, wherein R^7 and R^8 each independently represent a hydrogen atom, a straight or branched, optionally substituted lower alkyl group, or together form an alicyclic ring;

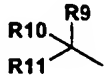
FOR CLAIM 1

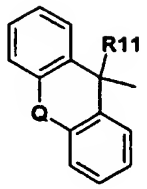
m is an integer from 0 to 8;

R^4 represents a lower alkyl group;

D represents a group of formula i) or ii)

i) ii)





wherein

R^9 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl;

R^{10} represent a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl or C_3-C_7 cycloalkyl;

and R^{11} represents a hydrogen atom or a hydroxy, methyl, or -CH_2OH group;

the cyclic groups represented by R^9 and R^{10} being optionally substituted by one or two substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, optionally substituted lower alkoxy, nitro, cyano, -CO_2R^{12} or –$NR^{12}R^{13}$, wherein R^{12} and R^{13} are identical or different and are selected from hydrogen and straight or branched, optionally substituted lower alkyl groups;

Q represents a single bond or a -CH_2-, -CH_2-CH_2-, -O-, -O-CH_2-, -S-, -S-CH_2- or -CH=CH- group;

FOR CLAIM 1

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

including all individual stereoisomers and mixtures thereof;

with the proviso that in those compounds wherein B is phenyl, R^9 is unsubstituted phenyl, R^{10} is unsubstitued phenyl or unsubstituted C_3-C_7 cycloalkyl, R^{11} is hydrogen or hydroxy, the sequence – $(CH_2)_n$ – A – $(CH_2)_m$ – is not one of methylene, ethylene or propylene.

2. A compound according to claim 1, wherein B represents a phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5, 6, 7, 8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl or benzothiazolyl group.

3. A compound according to claim 2, wherein B represents a phenyl, thienyl or pyrrolyl group.

4. A compound according to any one of the preceding claims wherein R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom, or a hydroxy, methyl, tert-butyl, -CH_2OH, 3-hydroxypropyl, -OMe, -NMe_2, -NHCOMe, -$CONH_2$, -CN, -NO_2, -COOMe or -CF_3 group.

5. A compound according to claim 4, wherein R^1, R^2 and R^3 each independently represent hydrogen, fluorine, chlorine or hydroxy.

6. A compound according to any one of the preceding claims wherein n = 0 or 1; m is an integer from 1 to 6; and A represents a -CH_2-, -CH=CH-, -CO-, -NMe-, -O- or -S- group.

7. A compound according to claim 6, wherein A is a -CH_2-, -CH=CH- or -O- group.

8. A compound according to claim 6, wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thien-2-ylpropyl, 4-oxo-4-thien-2-ylbutyl, 2-benzyloxyethyl, 3-o-tolyloxypropyl, 3-(3-cyanophenoxy)propyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 4-oxo-4-phenylbutyl, 4-(4-fluorophenyl)-4-oxobutyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(4-methoxyphenoxy)propyl, 3-(benzo[1,3]dioxol-5-yloxy)propyl.

9. A compound according to claim 8 wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)-4-oxobutyl or 3-thien-2-ylpropyl.

(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)

(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 1)

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 2)

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 1)

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 2)

(1*, 3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1)

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 2)

(1*, 3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 1)

(1*, 3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 2)

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1)

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2)

(1*, 3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1)

(1*, 3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2)

(1*, 3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-

R^5 and R^6 each independently represent a group chosen from a hydrogen atom, a straight optionally substituted lower alkyl group ~~or~~ and a branched~~,~~ optionally substituted lower alkyl group, or R^5 and R^6 together form an alicyclic ring;

n is an integer from 0 to 4;

FOR CLAIM 1

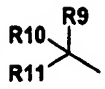
A represents a group chosen ~~selected~~ from $-CH_2-$, $-CH=CR^7-$, $-CR^7=CH-$, $-CR^7R^8-$, -CO-, -O-, -S-, -S(O)-, $-S(O)_2-$ and $-NR^7-$, wherein R^7 and R^8 each independently represent a group chosen from hydrogen atom, a straight optionally substituted lower alkyl group ~~or~~ and a branched~~,~~ optionally substituted lower alkyl group, or R^7 and R^8 together form an alicyclic ring;

m is an integer from 0 to 8;

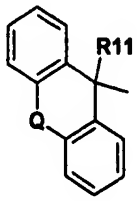
R^4 represents a lower alkyl group;

D represents a group of formula i) or ii)

i)



ii)



wherein

R^9 represents a group chosen ~~selected~~ from phenyl, 2-furyl, 3-furyl, 2-thienyl ~~or~~ and 3-thienyl;

R^{10} represents a group chosen ~~selected~~ from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl ~~or~~ and C_3-C_7 cycloalkyl;

and R^{11} represents a group chosen from a hydrogen atom, ~~or a~~ hydroxy, methyl, ~~or~~ and CH_2OH ~~group~~;

wherein each of the cyclic groups represented by R^9 and R^{10} ~~being~~ is independently optionally substituted by one or two substituents chosen ~~selected~~ from halogen, straight optionally substituted lower alkyl, ~~or~~ branched, optionally substituted lower alkyl, hydroxy, optionally substituted lower alkoxy, nitro, cyano, $-CO_2R^{12}$ ~~or~~ and $-NR^{12}R^{13}$, wherein R^{12} and R^{13} are identical or different and are each independently chosen ~~selected~~ from a hydrogen atom, ~~and~~ straight optionally substituted lower alkyl groups ~~or~~ and branched, optionally substituted lower alkyl groups;

Q represents a single bond or a group chosen from $-CH_2-$, $-CH_2-CH_2-$, -O-, $-O-CH_2-$, -S-, $-S-CH_2-$ ~~or~~ and ~~-CH=CH-~~ ~~group~~;

FOR CLAIM 1

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

~~including all~~ or an individual stereoisomers of a compound of formula (I) or ~~and~~ a mixtures of stereoisomers of a compound of formula (I) ~~thereof~~;

with the proviso that in those compounds of formula (I) wherein B is phenyl, R^9 is unsubstituted phenyl, R^{10} is unsubstitued phenyl or unsubstituted C_3-C_7 cycloalkyl, and R^{11} is hydrogen or hydroxy, the sequence $-(CH_2)_n-A-(CH_2)_m-$ is not one of methylene, ethylene or propylene.

2. (Currently amended) A compound according to claim 1, wherein B represents a group chosen from phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5, 6, 7,

8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl ~~or~~ and benzothiazolyl ~~group~~.

3. (Currently amended) A compound according to claim 2, wherein B represents a group chosen from phenyl, thienyl ~~or~~ and pyrrolyl ~~group~~.

4. (Currently amended) A compound according to claim 1, ~~any one of the preceding claims~~ wherein R^1, R^2 and R^3 each independently represents a group chosen from a hydrogen atom, ~~or~~ a halogen atom, ~~or~~ a hydroxy, methyl, tert-butyl, -CH_2OH, 3-hydroxypropyl, -OMe, -NMe_2, -NHCOMe, -$CONH_2$, -CN, -NO_2, -COOMe ~~or~~ and -CF_3 ~~group~~.

5. (Currently amended) A compound according to claim 4, wherein R^1, R^2 and R^3 each independently represents a group chosen from hydrogen, fluorine, chlorine ~~or~~ and hydroxy.

6. (Currently amended) A compound according to claim 1, ~~any one of the preceding claims~~ wherein n = 0 or 1; m is an integer from 1 to 6; and A represents a group chosen from -CH_2-, -CH=CH-, -CO-, -NMe-, -O- ~~or~~ and -S- ~~group~~.

7. (Currently amended) A compound according to claim 6, wherein A is a group chosen from -CH_2-, -CH=CH- ~~or~~ and -O- ~~group~~.
FOR CLAIM 7

8. (Currently amended) A compound according to claim 6, wherein the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group chosen ~~selected~~ from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thien-2-ylpropyl, 4-oxo-4-thien-2-ylbutyl, 2-benzyloxyethyl, 3-o-tolyloxypropyl, 3-(3-cyanophenoxy)propyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 4-oxo-4-phenylbutyl, 4-(4-

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 1);

(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereomer 2);

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 1);

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylallyl)pyrrolidinium bromide (diastereomer 2); FOR CLAIM 20

(1*, 3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1);

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 1);

(1*,3S)-1-[3-(4-Fluorophenoxy)propyl]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium chloride (diastereomer 2);

(1*, 3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 1);

(1*, 3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylpropyl)pyrrolidinium bromide (diastereomer 2);

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 1);

(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereomer 2);

(1*, 3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1);

(1*, 3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2);

(1*, 3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 1);

(1*, 3S)-1-Methyl-1-(3-o-tolyloxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)oxy]pyrrolidinium bromide (diastereomer 2);